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THESIS FOR THE DEGREE OF M.D.
on
OBSERVATIONS ON
THE DIAZO REACTION IN INFECTIVE CONDITIONS.

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INTRODUCTION.

In the year 1882 Ehrlich first described a new urine test which is now known as the Diazo reaction.

This test depends on the production of aniline colours, and it was claimed to be diagnostic, to a certain degree, in cases of Typhoid Fever and measles, in which diseases the reaction was found to be practically constant.

Numerous writers have added to our knowledge of the chemistry of this reaction, among others Loeper and Oppenheim have gone very fully into this part of the subject.

As the chemical side of the question hardly comes within the scope of this paper, I will merely give a few facts in connection with the reactions.

It appears that the colour reaction depends on the excretion of certain aromatic bodies, which are not normally found in urine, but which appear in Febrile and certain other conditions.

These aromatic bodies when acted on by the reagent used, give colours ranging from carmine to orange, through shades of pink.

According to Loeper and Oppenheim if Sulphanilic acid be acted on by nitrous acid diazo - sulfo - benzol is formed which unites with these aromatic bodies/

bodies to form these aniline colours.

In his original paper Erhlich used only two solutions, which consisted of I Sulphanilic acid and Sodium nitrite mixed. II. Liq. Ammon Fort or Caustic Soda Solution. The following is the exact method of Erhlich:-

I. A saturated solution of Sulphanilic acid (crystals) in 5 per cent Hydrochloric acid.

II. A $\frac{1}{2}$ per cent solution of pure Sodium Nitrite.

III. Liq. Ammon. Fort.

He recommended the solutions to be used as follows. A mixture containing Sulphanilic acid solution and the solution of Sodium Nitrite in proportion of 40 c.cm. of the former to 1 c.cm of the latter is put into a graduated tube and 10 c.cm of it added to an equal quantity of urine in a test tube. After shaking the mixture a drop of Liq. Ammon Fort is allowed to run down the side of the tube and the following occurs:-

I. A ring of red forms at the junction of the ammonia and the rest of the fluid

II. On shaking, the colour appears in the whole of the fluid in the tube.

III. If tube is shaken violently to produce a froth the/

the colour is imparted to the froth, the colour varying from carmine to pale pink.

- IV. After allowing the specimen so treated to stand for 24 hours a deposit forms which varies in colour from green to violet.

Erhlich specially mentioned that the pink colour must be imparted to the froth, otherwise the test is not positive.

Budden adds the following requirements.

- I. The test can only be performed during the day or by very white light.
- II. The urine should be less than 24 hours old and should be kept covered.
- III. Both the Sulphanilic acid and Sodium Nitrite being unstable deteriorate rapidly. Fresh solutions should be employed. The Sodium Nitrite should be renewed every week and the Sulphanilic acid should be less than a month old.
- IV. Accurate proportions of Sulphanilic acid and Sodium nitrite must be used to ensure success.

It is also of the greatest importance that the reagents themselves should be pure.

For practical chemical purposes I have found that/

that the use of three solutions is quite satisfactory and the method I have adopted is as follows:-

I used a test tube, graduated at 5 c.cm. and 10 c.cm. into this I poured 5 c.cm of urine then I added 5 c.cm. of the Solution of Sulphanilic Acid in Hydrochloric acid, and to this I added one drop of a $\frac{1}{2}$ per cent solution of pure sodium nitrite. I have also invariably followed Eudden's advice and violently shaken the mixture before adding the ammonia, as the froth is the most important part of the resultant mixture and its colour alone must be taken into account.

The difference in this procedure is in keeping the Sulphanilic acid and the Sodium nitrite in different bottles, and mixing them in the urine itself, and my results have quite justified this method.

There are certain fallacies, according to Loeper and Oppenheim which we must take into consideration; the urine of patients who are being treated with Antipyrine, Guaiacol or Creosote are said to give a colour resembling the diazo reaction.

Salol, naphthol, codeine and morphia may also cause confusion but not to such an extent as the first three drugs mentioned.

On the other hand Loeper and Oppenheim point out, /

out that there is no relation between indicanuria and the diazo reaction and this I shall again mention under Cerebro Spinal Meningitis.

They also found that neither the colour nor any of the usual constituents of the urine had any tendency to vitiate the results.

In a normal urine the colour change given by adding the reagents is sometimes very slight or a definite yellow or orange colour may appear.

Some observers have even included the orange colour, as part of the reaction, in their positive returns; but following Ehrlich's postulate that the reaction is negative unless a pink colour appears in the froth, I have in the following series of cases, counted such orange colour as negative.

I undertook this series of cases for the purpose of determining, if possible, whether this diazo reaction could be used in an infectious diseases Hospital to assist in the diagnosis of various infective conditions and whether it could at any time help in the prognosis of patients who were seriously ill.

In the Summary at the end, I have stated my opinion as to the value of this test.

TYPHOID FEVER.

Typhoid Fever is one of the diseases which was said by Erhlich to give the diazo reaction constantly and most of the work done on the subject has been in connection with this disease.

Erhlich in his original paper makes the following statements with regard to the presence of the reaction.

- I. That the reaction is one of the most constant signs from about the middle of the first week and if the reaction is negative, the diagnosis is doubtful.
- II. That in cases where the reaction is only slight or of short duration, the type of disease will be found to be mild.
- III. That the disappearance of the reaction is shortly followed by a remission of the temperature.
- IV. That the reaction cannot be used as a point in the diagnosis between Typhoid and Tuberculosis.

Rivier quoted by Loeper and Oppenheim found the reaction positive in 534, out of 550 cases examined and in another series 97 out of 100 cases were positive.

Osler and Mc.Rae give the percentage of positive reactions as 61. and Budden found it present in 17 cases out of 21.

My series of cases numbered 79 and with the exception of two cases an examination of their urine was/

was made on admission.

Of the 77 cases examined 67 gave a positive diazo, giving a percentage of 87.

The ten negative cases were admitted at various stages of the disease.

The following table gives the length of illness.

LENGTH OF ILLNESS.	NUMBER OF NEGATIVE CASES.
1 week or less	1
1 - 2 weeks	6
2 - 3 weeks	3

I have indicated the exact day on which each negative cases was admitted, graphically, in my chart of admissions.

It is interesting to note that three of the ten cases did not give a widal reaction in dilutions of 1.30 and 1.60 while the other 7 were positive to the widal test.

It will be noticed that not a single case gave a positive diazo with a negative widal. 74 of the cases admitted gave a history which could more or less be relied on.

LENGTH OF ILLNESS.	DIAZO POSITIVE.	DIAZO NEGATIVE.
1 week or less	20	1
1 - 2 weeks	34	6
2 - 3 weeks	9	3
3 - 4 weeks	1	0

It will be noticed that one case was admitted between the 3rd and 4th week with a positive reaction. I have included this case, as being ill for 28 days on admission and still giving a reaction it allowed us to make an unfavourable prognosis as a matter of fact he died.

As regards the earliest day on which the reaction may appear, Ehrlich says that the middle of the first week is the period at which it may be expected to be found.

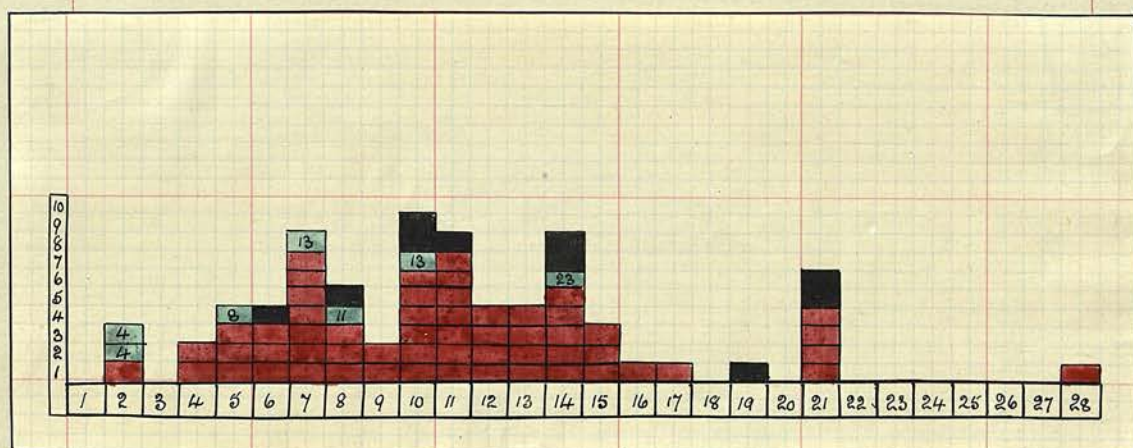
Ker mentions the second to sixth day as the earliest dates.

Loeper and Oppenheim examined 30 cases between the 3rd and 8th day and found the reaction positive in 28.

In the cases I examined three patients were admitted on the second day of disease and I found that one was positive while the other two, although negative on admission, gave a good reaction on the 4th day.

The/

The table below shows the exact number of cases admitted on each day of disease.



The Red squares refer to positive cases.
 The Black squares refer to negative cases
 The Green Squares refer to cases which were negative on admission and became positive later and the numbers attached indicates the days on which they became positive.

The/

The intensity of the reaction in Typhoid fever varies considerably. Some observers have recorded a reaction so intense that they have used the word "purple" to describe it.

I have never seen it so intense as this, in fact the majority of specimens have given the reaction in a slighter degree than in measles where the reaction is sometimes very marked.

When the reaction commences to fade it does not take long to entirely disappear, whereas in measles the reaction may remain to a slight degree for a considerable period.

In relapses the reaction is usually not so intense as in the primary attack, and as I mention later it does not last very long.

The length of time during which the reaction remains present varies very considerably.

Loeper and Oppenheim say that it usually disappears between the 12th and 15th day and that if it persists longer the case must be regarded as one of exceptional severity.

In the cases I had under observation the date of the disappearance of the reaction varied from the 9th day to the 32nd day.

Two of these cases were still positive on the 31st/

31st day of disease, one having been continuously positive during his fever and the other having two days with a negative diazo and again becoming positive.

19 other cases had still the reaction positive after three weeks illness and these were all fairly sharp cases.

10 cases retained the reaction till over the fortnight from the beginning of their illness the remaining cases became negative between the 9th and the 14th day.

The ten negative cases which were classified as true enteric, were all, with the exception of one, specially mild cases.

The severe case was absolutely negative all through her illness, not even the orange colour appearing in the froth which I have pointed out, is by some observers counted positive, as she had a swinging temperature for over three weeks after admission she must have been an early case.

The fact that these cases were nearly all mild proves that the severity of the case has a great influence on the diazo reaction being positive, and makes one believe that if in a case which is diagnosed as Enteric Fever we find the diazo reaction wanting, then we may assume that the case will be a mild one without complications.

It/

It is said that the diazo reaction returns in a relapse and of my cases I find that eight had relapses, and that six of these showed a return of the diazo during that period. I noticed that the reaction very soon became negative again, in fact they acted like a mild primary attack in which the reaction may be positive for only a few days.

It is of course, a well known fact that relapses are seldom if ever fatal. In the records of the City Hospital, Edinburgh, only one case died in a relapse, these records extend over a period of 25 years.

One of my cases had an irregular temperature in convalescence and this case did not give a positive reaction, and it would thus appear that the absence of the diazo with a return of the febrile symptoms would point to its not being a true relapse.

It is left for us to determine the value of the reaction in Diagnosis and Prognosis.

As regards Diagnosis then we may say, that as the reaction is fairly constant in Typhoid Fever its absence in a suspected case might make the diagnosis doubtful.

This is the opinion of Ker, who says "The chief value of the test is rather its absence than its presence/

presence, a case of continued fever, which at any time between the sixth and twelfth day, does not give the reaction is in all probability not a case of enteric fever. On the other hand if it is present, it is necessary to exclude the eruptive fevers, miliary tuberculosis and pneumonia, before assuming the case to be one of enteric."

Loeper and Oppenheim concur with this view in saying that the persistent absence of the diazo reaction between the 5th and 10th day of a febrile condition almost surely contradicts the diagnosis of enteric, and they add that a positive reaction is of less value as the test is positive in Typhus and in acute tuberculosis; both conditions which may be readily confused with enteric.

On the other hand Cameron says that its presence makes an additional unit in the sum of probabilities on which a diagnosis has often to be based.

Loeper and Oppenheim however allow that the reaction being often present before the widal reaction it may thus assist in the diagnosis.

My opinion is that it can at best be only of doubtful value in aiding the diagnosis and even then more by its absence than presence.

The fact that ten genuine cases of Enteric out of 77/

of 77 failed to give it, shows what difficulties we have to contend with in using it as a diagnostic agent.

In this connection I shall here mention the other diseases which were sent to the Wards of the City Hospital as Enteric Fever during the same period.

36 cases suffering from a variety of diseases were admitted; 30 of these were tested for the presence of the diazo and eight were found to be positive.

They were as follows:-

DISEASE.	NUMBER OF CASES POSITIVE.
Influenza.	1
Pneumonia.	1
Malignant Disease	1
Acute Tuberculosis	2
Kala - azar	1
Coli Infection	1
Septic Meningitis	1

The case of Kala-azar was of special interest as everything except the widal pointed to enteric fever, and being a disease seldom seen in this country, the fact that a vivid diazo reaction was obtained is worthy of note.

Among the other positive cases will be found one classified/

classified as coli infection. This case was not an enteric, but might have been an infection with a paratyphoid or some allied organism. The reaction in this case was very transient.

The following is the full list of cases admitted showing those negative and positive.

DISEASE.	NUMBER OF CASES.	DIAZO POSITIVE.
Influenza	9	1
Pneumonia	9	1
Malignant Disease	2	1
Pleurisy	1	0
Acute Tuberculosis	2	2
Tuberculosis Meningitis	1	0
Cerebrospinal Meningitis.	1	0
Septic Meningitis	1	1
Kala - azar	1	1
Coli Infection	2	1
Nothing Obvious	1	0

The Influence of the diazo on prognosis is interesting.

Osler and Mc.Rae say that the reaction may return with a relapse and this I have pointed out was found in some of my cases.

Rivier goes the length of saying that if the reaction reappears after having been absent for some days/

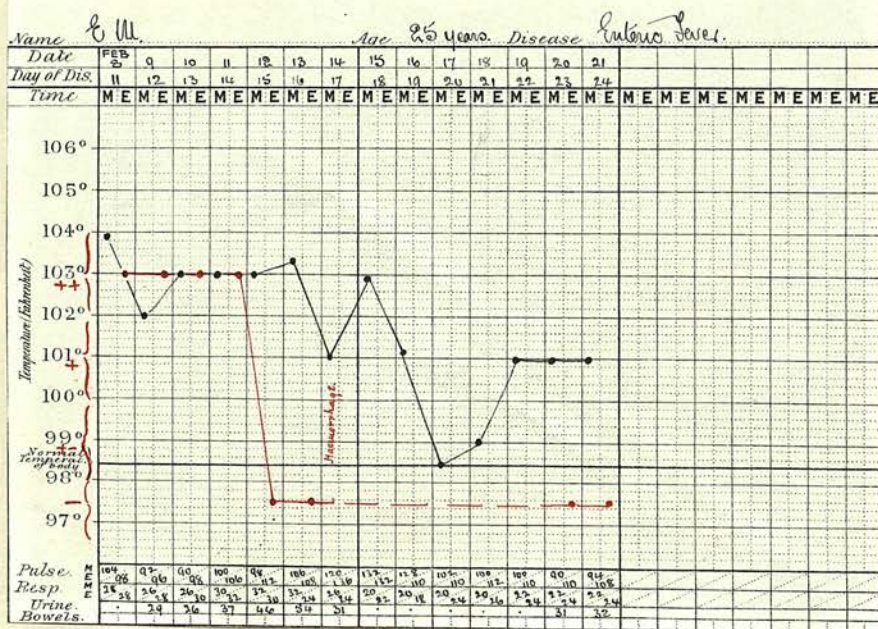
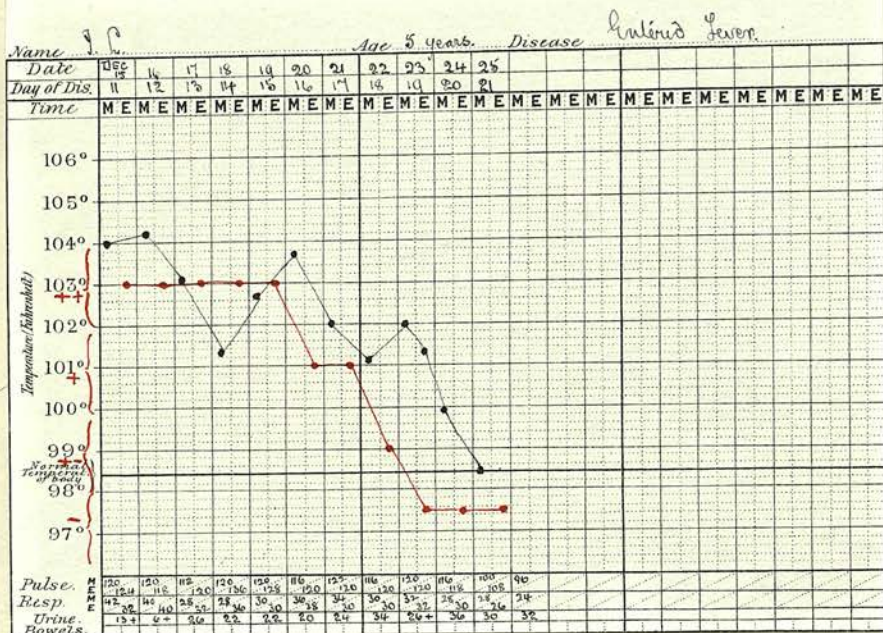
days, a relapse may be expected and that if it disappears before the temperature shows signs of falling some complication may be looked for.

Two of my cases go to prove this statement. Both of these cases had haemorrhages; and before the temperature showed any signs of falling the diazo vanished. In both cases the haemorrhage occurred within two days; in one case at any rate the haemorrhage was so severe as to cause great anxiety, a chart of one of these cases appears on the next page.

I think that possibly the disappearance of the diazo with a continuously high temperature ought to put us on our guard for possible complications.

Of the charts given below No.1 shows the usual curve of the temperature and diazo. No.2 shows a fall in the diazo followed by a haemorrhage.

For the purpose of demonstration, I have used Loeper's method of using the symbols ++, +, +-, -, to indicate the intensity of the reaction.



MEASLES.

In measles the diazo reaction is nearly always present.

Observers give different percentages of positive cases, but they are invariably high. In 90 cases collected by Héze the reaction was present in 79.

Osler and Mc.Rae give the percentage of positives as 80.

Budden found 18 positive out of 25 giving 72 per cent.

In a series of 100 cases I have just completed for this paper I found the reaction absent in only 11 cases.

As a rule the reaction does not appear until the rash is beginning to fade. This fact is mentioned by Ehrlich who states that the reaction may not be seen during the eruption stage but appears later. He explains this by saying that the materials required for the reaction are formed in the body during the Febrile period and excreted when the temperature commences to fall, as it does in measles when the rash commences to fade.

The fact that the reaction is usually negative for the first three or four days of the invasion period is unfortunate as it prevents the use of this/

this reaction for diagnosis.

As a matter of fact, in a certain number of cases, the reaction is positive before the rash appears, but it always gains its maximum intensity during the period when the rash is fading.

In my 100 cases, 10 gave a diazo reaction before the rash was fully out, and of these two were positive quite a day before any rash made its appearance, but this I think must be uncommon.

However as only 13 cases were admitted before the appearance of the rash, the percentage of positive results in the early part of the invasion period is relatively high.

It would be necessary to collect a larger number of cases : where the test was applied early in the disease before coming to a definite conclusion and as the majority of cases are admitted with the rash full out or fading this would entail a trial extending over a very considerable period.

On going more carefully into my results I found that the disappearance of the reaction showed no relation to the fall of the temperature; the reaction remaining present in a large number of cases for a long period often extending to over a week after the temperature had become normal. The urine/

urine of these cases being examined daily until the patients became convalescent.

On the other hand the actual height of the temperature seemed to have a slight but definite effect on the length of time the reaction remained present. Those whose temperatures were highest retained the reaction longest, and those who had no temperature or at most, only a slight degree of fever showed a very short positive phase.

The following table gives the exact figures.

TEMPERATURE	AVERAGE LENGTH OF POSITIVE PHASE.
104° and over	5 days
103° and 102°	3 days
101° and 100°	3 days
99° and 98°	1 day

There were of course notable exceptions and without doubt there is another factor which helps to determine the length of time the reaction remains positive. This factor may possibly be the tendency towards tuberculosis of localised tubercular lesions which are stirred into activity by the febrile processes.

After passing the stage of intense reaction which was as a rule greater than that found in other/

other diseases which give the diazo, the colour gradually fades from the urine, but a trace of pink may persist for many days after the patient has become convalescent. I mention this because I found that in Scarlet Fever on the other hand, the transition from an intense positive reaction to an absolute negative was one of the most remarkable and constant features.

As I have mentioned the retention of the reaction for a lengthy period ought to put us on our guard, and suggest to us the chances of a tubercular element.

The following case, which I made special notes on and which was not included in my series carries out this statement.

A girl age 11 years, who came in on the 1st or 2nd day of her invasion period, and who to my surprise gave a good reaction on admission; long before the rash appeared, still gave a good reaction on the 15th day. On making enquiries I found that she had a bad cough and had night sweats.

On examination of her chest I found an undoubted involvement of her right apex, and I have no doubt that this case retained the diazo for this lengthened period on account of the tubercular element present.

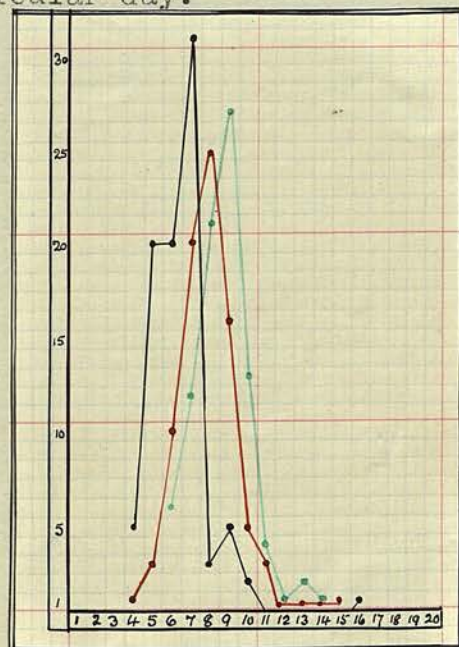
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The average day for the reaction to fade was the 8th or 9th, although several cases were still positive on the 11th, 12th or 13th day and one case only became negative of the 16th day, from the initial symptoms. This last case was also possibly tubercular.

The following chart indicates the relation between the disappearance of the Febrile period, the diazo reaction and the rash.

It shows that in the majority of cases the temperature was the first to become normal followed by the diazo reaction and lastly the rash.

The figures at the foot of the chart indicate the number of days ill, and the figures at the side show the exact number of cases which became negative on any particular day.



The black line represents temperature.
 The red line represents diazo reaction.
 The blue line represents rash.

Of the eleven negative cases I found that eight had either a normal or at most only slightly raised temperature, three however had a definite febrile period their temperatures being 104.8; 102.8; 101.

There was no apparent reason why these cases should be negative as they were all typical and had good rashes.

With regard to the eight cases with practically no temperature, the fact that they gave no reaction is in favour of the theory that in the majority of instances the excretion of the aromatic bodies depends to a large extent at any rate on the febrile processes and to the height of the temperature.

The majority of the cases were admitted with a fading rash, that is to say about the 5th day of the illness.

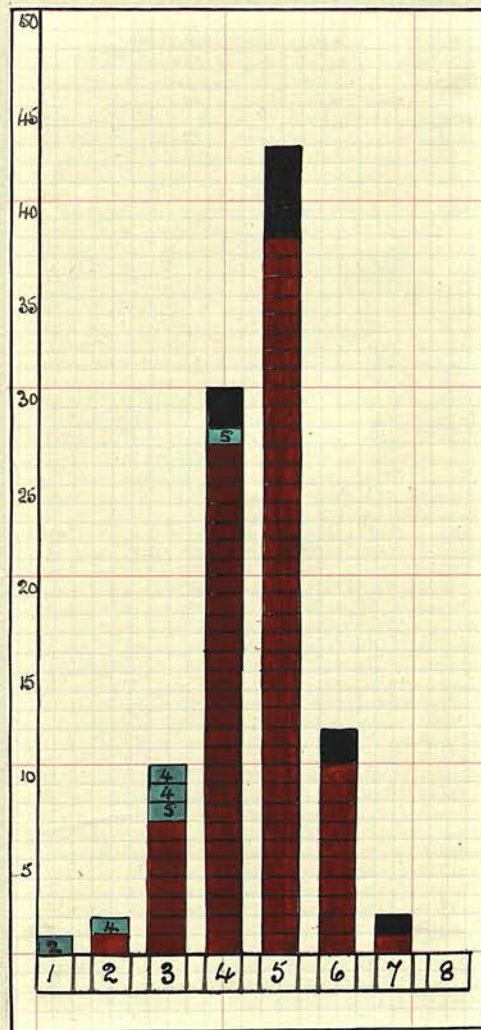
The following table which I have also shown in a graphic manner, indicates the number of cases admitted for each day of disease and the result of the diazo reaction on admission. It must be noticed however, that six changed from negative to positive on subsequent days.

NUMBER OF DAYS ILL.	REACTION +	REACTION -
1	0	1
2	1	1
3	7	3
4	27	3
5	38	5
6	10	2
7	1	1

N.B. 1 negative case admitted on the 1st day became positive on the 2nd.

1	"	"	"	"	"	2nd day	"	"	"	"	4th.
2	"	"	"	"	"	3rd day	"	"	"	"	4th.
1	"	"	"	"	"	3rd day	"	"	"	"	5th.
1	"	"	"	"	"	4th day	"	"	"	"	5th.

Chart showing relative number of positive and negative results in cases admitted on any day of illness, also number of case which were negative on admission and became positive later.



Total height of column represents total number of/

of cases admitted on each day.

The Black squares refer to negative cases.

The Red squares refer to positive cases.

The Green squares refer to cases which were negative on admission and became positive later. The number attached to the Green squares indicates the day on which that case became positive.

As I have before said, owing to the late appearance of the reaction in the majority of cases; the test is not of much practical value as far as diagnosis is concerned.

It would of course assist in the diagnosis if the reaction were found in an early case and therefore I think that the test should be tried in all early cases.

As regards differential diagnosis; there are three conditions in which the test might be of very special value.

- I. Loeper points out that it might be of value in distinguishing a post morbillous laryngitis from a true diphtheria, in which latter condition it is very rarely present.
- II. To distinguish German Measles from true Measles this reaction is said to be quite absent in German Measles.
- III. To distinguish a morbilliform antitoxin rash from the eruption of measles as the reaction is wanting in rashes due to antitoxin.

With reference to the diagnosis of measles from German Measles, I find that in a series of cases of German/

German measles, admitted to the City Hospital, Edinburgh of which special note was made by Dr. Ker, 37 out of 44 were absolutely negative, four gave a slight reaction and three were positive. This gives a positive percentage of 18.9 as compared with 89 per cent in true measles.

As regards the reaction in serum rashes I shall again mention this when I have to speak of rashes caused by serums

There is one further remark I should like to add, and that is in connection with the unfortunately common and fatal complications of measles: namely :- Bronchopneumonia, the reaction is very seldom present in this condition and I have no doubt that if the test is found to be positive a diagnosis of tuberculosis may be made.

I have been able to test a number of specimens from this condition, although not sufficient to bring any definite evidence to substantiate my statement; the difficulty of collecting specimens from children at the age when this complication is most common being very great.

SCARLET FEVER.

The diazo reaction has been described as occurring in Scarlet Fever in a varying proportion of cases.

Erhlich points out that it is only obtained occasionally.

Loeper and Oppenheim say that it is not uncommon in the febrile stage of the fever.

Rivier quoted by the above authors found the reaction present in twelve cases out of 29.

In a series of 190 cases examined for the reaction I found 58 cases positive, giving a percentage of 30.5. Of the 58 cases nine were obviously septic, that is to say Scarlatina anginosa and two of these died. No septic case which was examined gave a negative result.

On looking more closely at the clinical aspect of the cases I found that, if the severity of the attack could be estimated by the after complications, excluding of course nephritis, which may occur during the convalescence of the mildest cases, 16 were exceptionally severe and had either Rhinitis, Otorrhoea, Acute Adenitis or Arthritis and this gives a complication percentage for positive cases of 27.5. Apart from these cases with complications six others were/

were more than usually acute.

On the other hand only five of the positive cases were really mild and in these cases the reaction was not present to any marked degree.

Specimens from 55 of these cases were examined daily till the reaction had completely disappeared, till the temperature had fallen and the rash faded.

I noticed that the reaction disappeared much more suddenly than in measles, sometimes changing from a vivid positive to a complete negative in a day.

The remaining 132 cases were completely negative and of these only 18 or 13.6 per cent suffered from complications. There were some undoubtedly sharp cases among them, but not a single septic case and the mortality was nil.

The table below shows the nature of the complications occurring amongst positive and negative cases and it is noteworthy that Arthritis which is held to be an invasion of the specific organism of Scarlet Fever, was more common in the positive cases, while Otorrhoea which, as likely as not was a recrudescence of previous ear trouble was more prevalent in the negative cases.

NATURE OF COMPLICATION.	DIAZO POSITIVE.	DIAZO NEGATIVE.
Rhinitis	7	5
Arthritis	4	1
Otorrhoea	3	4
Adenitis	1	4
Rhinitis and Otorrhoea	2	4

This looks as if one could use the reaction in the prognosis of Scarlet Fever.

The presence of the reaction did not seem to have any marked relation to the severity of the rash, as quite a number of positive cases had slight rashes, and on the other hand in several of the negative cases the rash was well marked. This, of course is quite reasonable, as in Scarlatina Anginosa the brilliance of the rash has no relation to the severity of the throat lesions.

Neither had the height of the temperature any definite relation to the intensity or duration of the reaction, as about an equal proportion of positive and negative cases had high temperatures.

It would therefore appear that the toxæmia as seen by the constitutional symptoms and after complications had more effect on the reaction than anything else.

The/

The reaction itself is seldom so intense as in measles, and as a rule it passes off very rapidly, so that it is quite possible that a certain proportion of cases admitted after the fourth day might have previously given the reaction and already have become negative.

The following table shows the day of disease on which the cases became negative, and if we presume that the reaction appeared in each case at the commencement of the illness it will also indicate the number of days during which the reaction remained positive.

It will be seen that by the 6th day of the illness 40 out of 56 had returned to the normal.

DAY OF DISEASE.	NUMBER OF CASES NEGATIVE.
1	0
2	0
3	4
4	9
5	12
6	15
7	11
8	4
9	0
10	1

As regards the diagnosis of Scarlet Fever, I do not think the diazo is of any value, owing to its uncertainty. On the other hand, as I have pointed out under Serum rashes, its presence associated with a scarlatiniform eruption may help to guide us in coming to an opinion on the case; it may also serve to eliminate drug rashes.

In the Prognosis I think the reaction plays an important part. I consider that a case of Scarlet Fever giving a diazo reaction is more liable to have complications.

I have since completing my 190 cases, examined three more septic cases and found the reaction present in all. These cases are still in Hospital and I shall expect to find that if they recover, they will develop some further complications.

Table/

Table showing Scarlet Fever admissions for each day of disease, giving proportion of positive and negative cases on each day.

Total height of column represents number of cases admitted. Black represents negative and red positive cases.

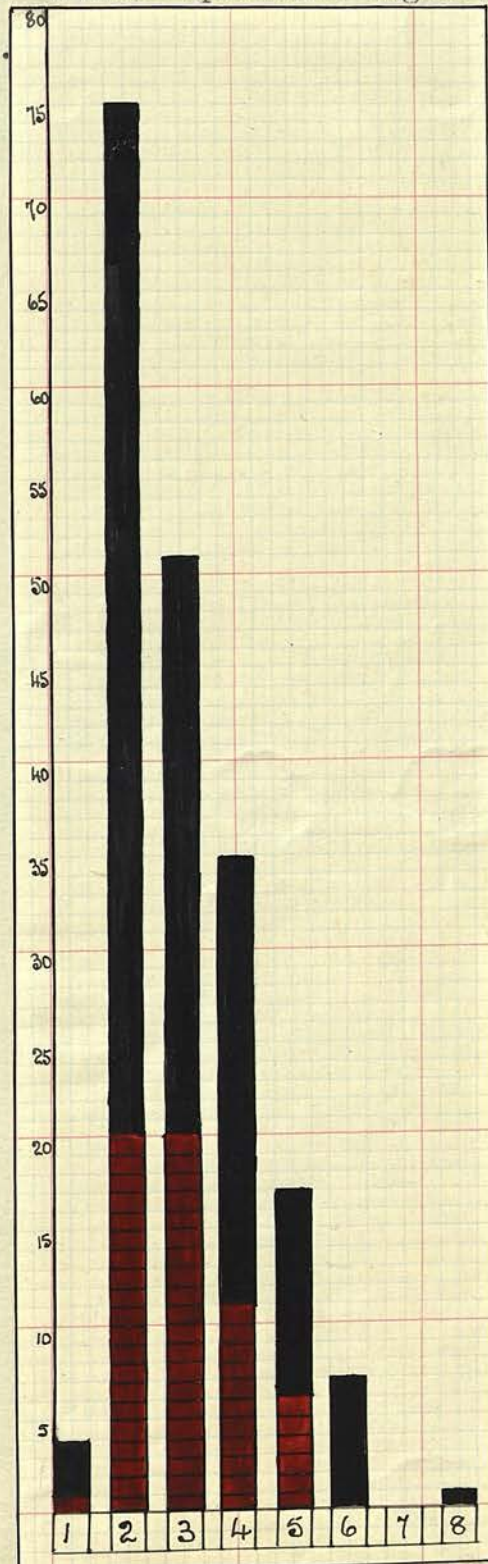
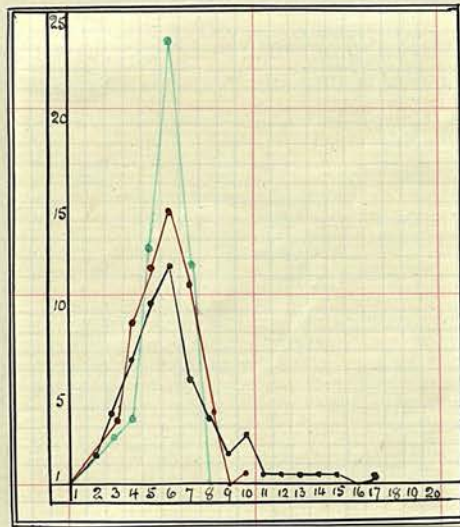


Chart showing the relation between the diazo reaction becoming negative, the fall of the temperature and the fading of the rash.

Based on observations on 56 cases.



Black refers to the temperature.

Red refers to the Diazo.

Green refers to the Rash.

The figures along the foot are day of illness.

The figures at the side indicate the number of cases.

Thus, on the 6th day of disease 12 cases had their temperatures normal for the first time, in 15 cases the diazo became negative and 24 cases had for the first time no signs of rash.

PULMONARY TUBERCULOSIS.

I want here to make a note on the frequency of the diazo reaction in Pulmonary Tuberculosis, as this disease can hardly be left out of a series of observations such as I have made.

The reaction in this disease has been very fully gone into by Budden, who examined 628 cases of Pulmonary Tuberculosis and found 83 positive; his cases were evidently in all stages of the disease some chronic and some acute; this I mention because my figures give such a much larger percentage of positive results. (namely 21 positive out of 50).

Erhlich found it present in 28 out of 55 cases of the disease.

According to the last named author it is the disease of all others which gives the reaction with a normal temperature, its presence indicates that the disease is advancing and the prognosis of cases giving the diazo appears to be bad.

Of my 21 positive cases nine have died, four are obviously dying and the remainder are all seriously ill, no case which gave the reaction has recovered.

Six cases which were negative have died, these cases were all examined a number of times and they had/

all tubercle bacilli in their sputa.

The fact that the reaction may be present one day and absent the next, makes it possible that some, at any rate, of these cases, were examined during the periods in which the diazo had become negative.

With reference to this Budden says:-

"It is probable that every fatal case of tuberculosis will yield the reaction at some period in its course."

"In view of the frequency of the intermissions we cannot say that any case is negative unless it has been tested constantly for long periods."

The difficulty of the diagnosis between Tuberculosis and Typhoid Fever I have already mentioned.

In a case which was sent in to the City Hospital as Typhoid I found the Diazo present, but on testing the specimens regularly, I found that instead of being constant from day to day as one would have expected in Typhoid, within certain limits, the reaction was extremely variable. The intensity varied, from day to day and there were days between when no reaction could be obtained.

In this, I think lies the difference between the reaction in these two diseases and one can say that in Typhoid when once present the reaction rarely fades/

fades until it disappears altogether, whereas in Pulmonary Tuberculosis the reaction may come and go: in relation to exacerbations of the Tubercular lesions.

In the case I above mentioned Tubercle Bacilli were found in the Sputum.

If we keep in view the possibility of cases giving the diazo which have a Tubercular History we may find an explanation of the appearance of the reaction in conditions in which we expect it to be negative.

ERYSIPELAS.

In Erysipelas it is uncommon to find the diazo reaction.

Erhlich puts this disease in the class of illnesses in which the reaction is found occasionally and he found it present in four out of seven examinations.

Loeper and Oppenheim quote Clemens who found it positive in five out of twenty-two cases and they say that severe cases frequently show it.

I have examined 18 cases and found the reaction present only once, and in this case the patient had a suspicious cough and spit, suggesting a tubercular element, although I was unable to demonstrate tubercle bacilli in her sputum.

The patient in question was not specially ill and made a good recovery without any complications.

Only one of the 18 patients died and he was quite negative, specimens being examined from time to time.

Loeper and Oppenheim point out the value of the diazo in prognosis in Erysipelas. They say if present in a severe case its sudden disappearance is of evil omen.

I have not been able to verify this statement as/

as the only case which died suffered from an inter-current affection, which was the ultimate cause of his death.

In diagnosis the test is of course of no value.

DIPHTHERIA AND SERUM RASHES.

Diphtheria is one of the diseases in which the reaction is said to be quite negative. Lobligeois quoted by Ker, puts on record 118 cases of diphtheria with one positive reaction.

Erhlich tested nine cases with one positive and that only a trace.

In the series of cases which I examined, numbering 20, I found the reaction present in only two cases; In both these cases the reaction was only slight and there appeared to be no other cause for the reaction being present except the diphtheria. The reaction was very transient both specimens being negative the day following.

As I mentioned under measles, the only use we can put the reaction to in diphtheria is in distinguishing a post-morbillous Laryngitis in which the reaction might be present from a laryngeal diphtheria.

Its presence also in a case sent to Hospital as diphtheria and suspected to be scarlet fever, would strengthen our diagnosis of the latter disease.

SERUM RASHES.

Lobligeois has pointed out the value of the diazo reaction in distinguishing rashes due to antitoxin from Scarlet Fever, and as a large percentage of these serum rashes resemble measles, the test is doubtless of value in distinguishing these conditions also.

As to the Scarlatiniform antitoxin rashes, we must remember that as the reaction is only occasionally found in scarlet fever (in my cases 58 cases out of 190), the fact that a patient with rash has a negative diazo does not for that reason allow us to make any definite diagnosis, but if the patient has a positive reaction then we may practically say that the rash is not due to antitoxin.

In measles the diazo being positive in 80 to 90 per cent of cases; the fact that a child with a morbilliform rash does not give the reaction, should help to eliminate measles from the diagnosis.

Serum rashes are not nearly so common as formerly and it is difficult to collect a sufficient number of cases to be of any value.

I have been able to test specimens from 14 patients with antitoxin rashes. 13 of these rashes were due to antidiphtheritic serum and one to anti-meningococcic serum. These I have classified as Scarlatiniform, /

Scarlatiniform, morbilliform and urticarial.

The following results were obtained:-

NATURE OF RASH.	DIAZO POSITIVE.	DIAZO NEGATIVE.
Scarlatiniform	0	3
Morbilliform	0	5
Urticarial	1	5

We see from this that all those cases with rashes resembling Scarlet Fever or Measles were negative, while one out of five of the urticarial cases was positive.

The positive case had practically no constitutional symptoms and no rise of temperature and I could not find out any reason for the reaction being positive.

It is quite evident that the number of cases under observation was too small to come to any definite conclusion as to the complete absence of the reaction in serum rashes resembling scarlet fever and measles; but I think that in a diphtheria ward where a patient has a rash with a certain amount of constitutional symptoms the urine ought to be tested for the diazo, as the result might aid considerably in diagnosis.

CEREBROSPINAL MENINGITIS.

The diagnosis of meningitis caused by the diplococcus intracellularis meningitidis from other types of meningitis being of considerable importance it would be of considerable help if the diazo reaction could give us a clue to the exact condition.

Erhlich holds that diseases of the spinal cord are always negative to the reaction and I found that cerebrospinal meningitis was no exception.

I tested specimens from ten cases from whose fluid I had isolated the diplococcus intracellularis and I found them invariably negative.

As I have mentioned before, certain observers have found that there is no connection between Indicanuria and the diazo reaction and as all of these cases showed a great increase of indican in their urine, I must concur with this view.

It is then left for us to enquire into the state of affairs in other types of meningitis.

Budden in his exhaustive article on the diazo reaction in tubercular conditions states that he examined six specimens from cases of tubercular meningitis and found the reaction present in all to a marked degree. Five of his cases were proved to be that disease at the post mortems.

This is interesting, because it follows that
if/

if in a case of suspected cerebrospinal meningitis the diazo is positive then we may exclude that disease.

However, further work must be done on this subject before coming to a very definite conclusion, as both my cases of Tubercular meningitis were negative.

The following table shows the cases of meningitis I have examined and the results.

NATURE OF DISEASE.	NUMBER OF CASES.	POSITIVE RESULTS.
Cerebrospinal Meningitis	10	0
Tubercular Meningitis.	2	0
Septic Meningitis	2	1

SUMMARY OF CASES EXAMINED FOR THE DIAZO REACTION.

DISEASES.	NUMBER OF OF CASES.	NUMBER POSITIVE.
Typhoid Fever	77	67
Measles	100	89
Scarlet Fever	190	58
Erysipelas	18	1
Diphtheria	20	2
Serum Rashes	14	1
Chickenpox	2	0
Smallpox	4	2
Cerebrospinal Meningitis	10	0
Septic Meningitis	2	1
Tubercular Meningitis	2	0
Acute Miliary Tuberculosis	2	2
Pulmonary Tuberculosis	50	21
Pneumonia	9	1
Pleurisy	1	0
Influenza	9	1
Kala-azar	1	1
Purpura Haemorrhagica	1	0
Coli Infection	2	1
German Measles	1	0

CONCLUSIONS.

As we have seen by the foregoing pages this reaction occurs in a variety of conditions and it remains for me to add my opinion as to the usefulness of the test in diagnosing infective conditions and in giving a prognosis in serious cases.

As regards diagnosis we have to look at several groups of cases.

In the first group I have placed Typhoid and Tuberculosis.

In Typhoid the reaction is present in 80 - 90 per cent of cases, it occurs early and falls as a rule with the lysis; during the period of fever, the reaction is as a rule continuous.

In Tuberculosis on the other hand the reaction occurs only in advancing cases of pulmonary tuberculosis, in acute Miliary Tuberculosis and in Tubercular Meningitis. The reaction may vary in intensity or may disappear without the temperature falling or it may be present with a normal temperature.

We see by this that its presence at any rate is not of much value; its absence on the other hand may help to exclude Typhoid but not absolutely, especially in mild cases, therefore the presence or absence of the reaction in a suspected case can only be/

be of slight value, the test therefore should not be relied on.

The second group consists of Measles, German measles and Morbilliform antitoxin rashes, here there may be distinct uses in the reaction for we have seen that over 80 per cent of true measles give the reaction, and that it hardly ever occurs in German measles, while it is entirely absent in antitoxin rashes.

Taking the first two conditions, namely Measles and German Measles, I will illustrate the value of the test by an actual case.

A patient sent in to this Hospital as measles with a fading rash appeared so doubtful that she was isolated. The symptoms had been rather slight and the parents had not taken much notice of them and could not speak with certainty about them. On examining the urine I found the reaction wanting and the patient was kept in isolation. Had the reaction been positive, I have no doubt that she would have been classified as a measles; as a matter of fact we regarded her as a case of German Measles.

As regards measles and antitoxin rashes, the reaction might be of distinct value for if we find the reaction present in a case which presents the appearance/

appearance of measles it is probable that the patient is suffering from that condition.

I have already pointed out the value of the test in differentiating between a post morbillous laryngitis and diphtheria, and here again the test has a distinct value.

The next group consists of Scarlet Fever on the one hand and Scarlatiniform eruptions due to any other cause on the other, the presence of the reaction pointing to the former condition.

Lastly we have cerebrospinal and tubercular meningitis, the absence of the reaction is quite definite in the former condition, while certain observers have found it constantly present in the latter disease. If this is so, then I think there is an opening for the diazo in distinguishing between a case of cerebrospinal meningitis in which for some cause no fluid can be obtained by lumbar puncture and Tubercular Meningitis.

In Prognosis, the diazo may be of considerable use.

In Typhoid Fever a sudden disappearance of the reaction with the temperature showing no tendency to fall, indicates the approach of some complication. This is shown well in the case I have mentioned which developed/

developed a haemorrhage after the diazo had suddenly vanished. It is also a fact that cases which retain the reaction for a long period are more serious than those which are positive for only a short time, and on the other hand a genuine Typhoid without a diazo reaction may be classed as a mild case.

In Scarlet Fever as I have pointed out under the observations made on that disease, the severe cases give the reaction most commonly, and the really dangerous cases (*Scarlatina Anginosa*) are almost invariably positive.

Complications occur more commonly in the cases which give reaction more especially arthritis.

In Measles the diazo, being so constant, has no influence on the prognosis, but undoubtedly the presence of the reaction is a post morbillous Bronchopneumonia indicates that the disease is terminating in Tuberculosis, it is therefore an unfavourable sign to find it present in this condition.

As regards Erysipelas, it is said that cases where the reaction is found, it is a bad sign if the test becomes negative without the patient showing signs of general improvement.

In/

In conclusion I may add that as the test is so easy to carry out, I think that it should be employed more commonly. It has distinct uses, both in diagnosis and in prognosis and its presence or absence may be of value in diagnosing doubtful cases, and in affording grounds, for giving a definite prognosis.

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